Journal of Human Genetics (2016) 61, 3–4

www.nature.com/jhg

COMMENTARY

# Atrial fibrillation: an inherited cardiovascular disease—a commentary on genetics of atrial fibrillation: from families to genomes

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*Journal of Human Genetics* (2016) **61,** 3–4; doi:10.1038/jhg.2015.63; published online 11 June 2015

## ATRIAL FIBRILLATION AS AN INHERITED CARDIOVASCULAR DISEASE

The fraction of the risk for atrial fibrillation (AF) attributable to established factors (hypertension, smoking, obesity, diabetes mellitus, age, male sex and heart disease) is roughly 50% with hypertension being the most prominent modifiable risk factor.[1] On the other hand, it has been shown that at least 5% of all patients with AF and 15% of those with only AF but without established clinical risk factors for AF had a positive history of AF.[2] These facts have motivated researchers to investigate the risk of AF among those with documented familial AF, as well as genome-wide association studies (GWASs) that have screened for common single-nucleotide polymorphisms (SNPs) associated with AF.[3] In this issue of the journal, Christophersen *et al.*[4] have nicely summarized the current understanding of genetics in AF from rare variants to common variants. We acknowledge that AF is heritable; however, most cardiologists do not routinely collect information on family history of AF, nor do they use this information for decision-making in clinical practice due to the lack of evidence. Thus, future clinical trials are needed to verify the clinical utility of family history information of AF beyond established risk factors in the first place. The next step could be genotype–phenotype association studies regardless of allele frequency. Finally, one of the possible tentative goals of genetics in AF could be to develop a risk calculator for AF based on human variations. Such approaches have already been applied in AF. For example, an AF genetic risk score comprising 12 common genetic variations was as powerful as hypertension to estimate AF events.[5] However, further studies with larger samples, and with multiple ethical perspectives, are needed to be accepted as a common clinical practice to investigate such genetic risk scores. Another possible goal could be to find novel molecules as therapeutic targets, as has been shown with lipids. In this regard, whole-exome sequencing (WES) has emerged as a promising tool for gene discovery in families with suspected monogenic (or polygenic) disorders, with a success rate exceeding 20%.[6] In general, hundreds or thousands of variants are found in an individual through the WES approach.[7] Then, typically, the variants predicted as benign, common and unmatched assuming co-segregation should be excluded. In this process, great advances have been made in the fields of *in silico* variant annotation prediction and in the information of allele frequency of a certain variant based on huge collaborative efforts in exome-sequenced data sets publicly available.

## AF AS AN ION CHANNEL DISEASE

Since the first gene (*KCNQ1*) responsible for familial AF was identified in 2003, many variants in genes encoding ion channel subunits, cardiac gap junctions and signaling molecules have been identified in monogenic AF families. These genetic variants predispose individuals to AF by enhanced or delayed atrial action potential repolarization, conduction velocity heterogeneity, cellular hyperexcitability and hormonal modulation of atrial electrophysiology.[8] Once a susceptibility variant is identified, it is important to identify the mechanistic links between the variant and disease expression. The

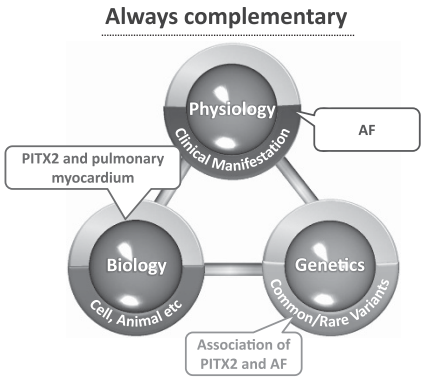


**Figure 1** Schema of physiology, biology and genetics. Investigations of physiology, biology and genetics are always complementary, and have contributed to our understanding of AF. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

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functional role of ion channel gene variants in AF can be usually assessed by a cellular electrophysiological study using a heterologous expression system. In addition, elucidating the molecular mechanisms of AF may allow a mechanism-based approach for treatment to be developed. For example, patients with gain-of-function ion channel variants are likely to benefit from a drug that selectively blocks mutant channel complexes. WES applied to familial AF kindreds or lone AF patients will identify many rare variants of different types of genes, and the true causal allele should be identified from the large number of insignificant alleles. To link these variants to a clinical phenotype, a family study, as well as functional evaluation, is required using a model system including zebrafish, mice or patient-specific induced pluripotent stem cells.

## PHYSIOLOGY, BIOLOGY AND GENETICS OF AF

In 1998, Häissagurre *et al.*[9] demonstrated that pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of AF. After this report, myocardial sleeve, in which paired-like homeodomain transcription factor 2 (*PITX2*) has a key role in its formation, has been shown to initiate AF. In 2009, a GWAS identified a strong association between SNPs in the *PITX2* gene and AF.[10] Each of these investigations contributed complementarily to our understanding of AF (Figure 1).

## CONCLUSION

Given the development of novel genotyping and sequencing technologies, as well as extensive catalogs of human genetic variation together with functional analyses, cardiologists are now realizing that AF is highly heritable. Rigorous efforts are currently underway, and it is highly likely that these efforts could reveal the contribution of rare and common variants to the overall genetic architecture of AF in the next few years.

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